REMARKS

Amendments

Unelected claims 10-13 and 17 are canceled. Unelected claims 18-20 are subject to rejoinder, hereby requested. Claim 1 is amended to provide formal antecedents for "the termination codon" and the final intron". These amendments do not change the scope or subject matter of the claims, and introduce no new matter.

Non-statutory Double Patenting

Upon an indication of allowable subject matter, claims 4 and 5 will be canceled, or alternatively, a terminal disclaimer will be submitted.

35USC103 (a)

Chu and Prockop describe natural collagen genes and proteins. Olsen is an early description of naturally cleaved C-terminal collagen propeptide. As there is no dispute that procollagens, including their natural propeptide terminal portions are known in the art, the issue here is what Carter suggests in view of these known, natural procollagen compositions.

Virtually all therapeutically significant recombinant proteins such as insulin, human growth hormone, etc. are produced in E. coli bacteria. Frequently, the bacteria will only express these foreign proteins at negligible levels or as insoluble inclusion bodies rather than useful, secreted product. The most common solution to this problem has been to express the foreign protein as a fusion with an N-terminal native E. coli secretory protein, isolate the resultant fusion protein and then cleave off the native E. coli N-terminal portion to obtain the therapeutic, typically human protein. The Carter reference reviews enzymes for cleaving recombinant proteins from their fusion partners. In his first paragraph, Carter reports that N-terminal fusions are used to facilitate expression of heterologous target proteins in E. coli bacteria, and that the N-terminal fusion partner may also be chosen to provide an "affinity handle" for subsequent purification using a high affinity ligand of the handle.

An affinity handle is a polypeptide with a high affinity for a particular ligand. Carter reports that at least a dozen different affinity handles have been used in the purification of fusion proteins (Carter, p.181, first paragraph; see also, Carter, p.182, Fig.1; A248-A249). In his survey of enzymes used for site-specific proteolysis (Carter, p.185-190; A252-257), Carter provides four

tables of exemplary fusion proteins (Carter, Tables II, III, V, and VI; A252-255). These fusion proteins comprise a mammalian protein-of-interest fused to a bacterial protein, wherein the latter provides functionalities like enhanced expression (e.g. cII, trpE), a label (e.g. β-gal, CAT), or, as relevant to this appeal, an affinity handle (e.g. Protein A, MBP) (each of these fusion partners is recited in Carter's Table II; A252).

Carter's exemplified affinity handles are well-established in the art of protein purification by chromatography, which is the art of separating fluid mixtures by selectively adsorbing components on a stationary phase. For example, Protein A has high affinity for its ligand, the Fc portion of IgG antibodies; hence, one can purify Protein A (or fusion proteins comprising a Protein A moiety), for example, by adsorbing the proteins to a bead or surface coated with IgG Fc fragments. Similarly, MBP has high affinity for its ligand, the sugar maltose, and one can purify MBP (or fusion proteins comprising an MBP moiety) by adsorbing the proteins to a bead or surface coated with maltose.

That is the cited art. Our claims require a recombinant procollagen chain having a natural collagen chain separated from a natural procollagen C-terminal propeptide by a non-native cleavage site. These recombinant, synthetic procollagens facilitate post-translational removal of the propeptides in environments lacking the proteases specific for the native procollagen. Our claims have nothing to do with affinity handles.

The way the rejection applies Carter is to reason that it would have been obvious to make the claimed recombinant collagen because the required natural procollagen C-terminal propeptide could be used as an affinity handle to purify the collagen. Is this reasoning rational? Would one skilled in the art really consider using a natural procollagen C-terminal propeptide as a recombinant affinity handle to purify collagen? In fact, purifying collagen is a simple matter because collagen specific antibodies are readily made and widely commercially available, e.g. Sigma-Aldrich Catalog Nos. C8471 and C1962 (Request for Rehearing, p.2, lines 14-15; A44, lines 14-15). The skilled artisan just directly affinity purifies the collagen with these antibodies. That is why the antibodies are sold. Affinity handles are a clever but extraordinarily expensive solution to the problem of not having access to specific antibodies to your target protein. When as here, specific antibodies are readily obtained or produced, there is simply no rational application of affinity handles.

But suppose there were no available collagen-specific antibodies (there are) and suppose there was no way to easily make them (there is). Under this non-existent scenario, it might not be possible to directly isolate the collagen, and it might make sense to instead genetically engineer onto the collagen an affinity handle as described in Carter, then use a handle-specific antibody to adsorb the fusion protein, and then use one of Carter's specific proteolysis techniques to cleave off the affinity handle. As noted by Carter, there are at least a dozen known affinity handles which have high affinity ligands which can be used for purification, such as the Protein A and the MBP exemplified in Carter. Hence, under this fictional scenario, one skilled in the art might use genetic engineering to construct a collagen - Protein A fusion, adsorb the fusion proteins on immobilized IgG Fc fragments, and then proteolytically cleave off the Protein A affinity handle to liberate the collagen.

However, even conjuring this non-existent scenario, we have still not managed to reconstruct our invention, which requires not an affinity handle, but a natural procollagen C-terminal propeptide. To reconstruct our invention, we must further disregard what Carter means by an affinity handle. Carter refers to "at least a dozen" known affinity handles, which are polypeptides "with a high affinity for a particular ligand." He exemplifies these with Protein A (having a high affinity for IgG Fc fragments) and MBP (having a high affinity for maltose). Natural procollagen C-terminal propeptides are not affinity handles: they do not have a high affinity for a particular ligand and no one skilled in the art, Carter included, has ever deigned to characterize them as such.

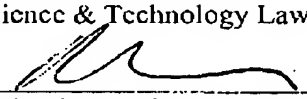
The Action does not recite any rational path by which one skilled in the art would begin at the cited art and arrive at our invention. When one skilled in the art seeks to affinity purify collagen, she makes or buys collagen-specific antibodies and purifies it. If we fictionalize and suppose that such antibodies are not available or produceable, one skilled in the art might resort to using genetic engineering to put an affinity handle on the collagen and use the ligand of that handle to purify the collagen. However, even in this fictional world, the skilled artisan would use one of the dozen or so known affinity handles having known ligands, such as protein A. The rejection requires that the skilled artisan instead put on a natural collagen propeptide, which is not an affinity handle, and which has no known ligand. Why would one skilled in the art arbitrarily select as her "affinity handle" something which has no known ligand? Why would one skilled in the art even be engaging in all this complex genetic engineering, affinity labeling

and proteolytic processing to purify a protein, when specific-antibodies to that protein are readily available? Under our facts, there is no rational or scientifically plausible scenario in which a scientist would journey from the cited art to our invention.

We recognize that with the benefit of hindsight, the present invention may appear to one outside the art to be a logical solution to the problem of expressing recombinant collagen in systems which do not naturally express the requisite procollagen-modifying enzymes. In fact, re-engineering the procollagen gene as disclosed was unprecedented and contrary to the way the problem was being addressed by those skilled in the art. Prockop II (A261-A298), for example, purports to describe production of recombinant collagen in a variety of cell types, including cells, such as yeast cells, which do not naturally produce the necessary post-translational processing enzymes. Prockop's solution is the conventional one: to modify the expression system – not the gene-of-interest. Specifically, Prockop II proposes to engineer the cells so that they will express the necessary processing enzymes (Prockop II at p.9, lines 7-12; A270). Nowhere does any of the cited art, Prockop II included, ever suggest mutating the collagen genes to facilitate processing. Their singular teaching away from our strategy of engineering the collagens themselves is more directly relevant to what was obvious to those skilled in the art at the time the invention was made than is any hindsight reconstruction of our invention.

The subject claims further require that the recombinant procollagen polypeptide chain further comprise "a second propeptide and a second non-natural site-specific proteolytic agent recognition site, wherein said second non-natural site-specific proteolytic agent recognition site is located between said collagen chain and said second propeptide". As noted by the Board reversing a similar rejection in the parent case, "[W]e see no reason, and the examiner failed to identify a reason in the art, to suggest that a person of ordinary skill in the art would modify the references to include a second propeptide and a second non-natural site-specific proteolytic agent recognition site." Decision dated Apr 30, 2001; Appeal No. 1999-2231; Appl. No. 08/278,774).

Respectfully submitted,
Science & Technology Law Group



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